Molecular Biology and Pharmacology of α_1-Adrenoceptors

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Adrenoceptor Pharmacology: Urogenital Applications

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Abstract
Although the selective α_1-adrenoceptor antagonists were initially developed as antihypertensive drugs, and they are still utilized for this indication, the α_1-adrenoceptor blockers are now used extensively for the symptomatic treatment of benign prostatic hyperplasia (BPH). As a result, a number of new drugs in this class have been specifically developed for use in BPH. The utility of α_1-adrenoceptor antagonists in BPH derives from the observation, made several decades ago, that the irreversible, α_1-adrenoceptor selective antagonist phenoxybenzamine, blocked the contractile activity of norepinephrine in isolated strips of rat or human prostate. Following the further subclassification of α_1-adrenoceptors into the α_{1A}-, α_{1B}- and α_{1D}-adrenoceptor subtypes, the relationship between subtype selectivity and efficacy in BPH has been investigated in the hope of developing more selective drugs for the treatment of this disorder. Molecular characterization of the adrenoceptor population in human prostate clearly shows the α_{1A}-adrenoceptor subtype to predominate, and highly selective α_{1A}-adrenoceptor antagonists have been identified and investigated in BPH. However, controversy remains as to whether prostatic smooth muscle contraction is mediated by the α_{1A}-adrenoceptor, or by another novel α_1-adrenoceptor subtype (not corresponding to any of the three known recombinant α_1-adrenoceptors), or both. α_1-Adrenoceptor agonists have been used clinically for the treatment of stress incontinence, acting to increase urethral tone by contracting urethral smooth muscle. Research efforts are ongoing to identify agents of this class having a selective action on urethral versus vascular smooth muscle, in order to produce a greater effect on the urethra without producing dose-limiting increases in blood pressure. Local administration of vascular smooth muscle relaxants, either alone or in combination, has been used for the treatment of erectile dysfunction. An α_1-adrenoceptor antagonist is often used as one component in such mixtures, which act to relax trabecular smooth muscle. The recent demonstration that a systemically administered drug can produce a sufficiently selective action on cavernosal smooth muscle to allow efficacy without producing limiting systemic side effects has renewed interest in the possibility of systemic administration of α_1-adrenoceptor antagonists for this indication.

Role of α-Adrenoceptors in Urogenital Smooth Muscle

It has long been known that activation of α-adrenoceptors will produce contraction of prostatic, urethral and cavernosal smooth muscle. Under most conditions, bladder smooth muscle is relatively unresponsive to α-adrenoceptor activation inasmuch as the predominant adrenoceptor in this tissue is the β-adrenoceptor which mediates relaxation. Although mRNA and protein for the α_2-adrenoceptor can be detected in these urogenital tissues, most

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studies have shown that α-adrenoceptor mediated contraction involves predominantly, if not exclusively, the α_1-adrenoceptor subtypes.

It is now established that there are three subtypes of the α_1-adrenoceptor [1–2]. These have been designated as α_{1A}, α_{1B} and α_{1D}. The possibility of additional α_1-adrenoceptor subtypes has not been excluded, although extensive efforts have not to date resulted in the cloning of any additional α_1-adrenoceptor subtypes. However, an additional putative novel α_1-adrenoceptor subtype, commonly designated as the α_{1L}-adrenoceptor, has been proposed to exist, based on physiological responses in a variety of tissues, and this receptor has been suggested to play an important role in the contraction of prostatic and urethral smooth muscle.

Prostate

The role of the α_1-adrenoceptor subtypes in the contraction of prostatic smooth muscle has been studied extensively. Localization of mRNA for the three α_1-adrenoceptor subtypes in human prostate demonstrated that the α_{1A}-adrenoceptor predominanted in this tissue [3–4]. Studies comparing the functional potencies of α_1-adrenoceptor antagonists in inhibiting agonist-induced contraction in the human prostate with their affinities for the recombinant α_1-adrenoceptor subtypes generally shows a good correlation with their affinities for α_{1A}-adrenoceptors. By contrast there is typically a lack of correlation with affinities for α_{1B} and α_{1D}-adrenoceptors [5–7]. These findings have led to the design of highly selective α_{1A}-adrenoceptor antagonists for use in BPH. However, in most studies correlating antagonists affinities in human or animal prostate with affinities for the recombinant α_{1A}-adrenoceptor, typically some compounds remain significantly outside of the correlation and show substantially weaker functional potency in prostatic tissue than would be predicted by their affinities for the α_{1A}-adrenoceptor [7–10]. These findings are consistent with the existence of an additional α_1-adrenoceptor subtype which may contribute, at least in part, to the response in the prostate.

Urethra

The receptor responsible for urethral contraction is likely to have similar characteristics to that of the prostate. Comparison of the human urethra and prostate showed similar pharmacological profiles for a number of α_1-adrenoceptor antagonists, and the distribution of α_1-adrenoceptor mRNA was similar between the two tissues [11]. Accordingly, NS-49, a selective α_{1A}-adrenoceptor agonist, produces selective increases in urethral pressure vis-a-vis systemic blood pressure when administered intravenously to the anesthetized dog [12]. However, as was observed for the prostate, unexpectedly low affinities for certain α_{1A}-adrenoceptor antagonists have also been observed in the urethra [13], and characterization of the contractile response to norepinephrine in the rabbit bladder neck also shows a pharmacological profile that would suggest the possible existence of the α_{1L}-adrenoceptor [14].

Corpus cavernosa

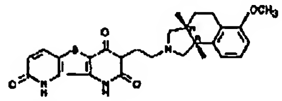
mRNA for all three of the α_1-adrenoceptor subtypes is present in the corpus cavernosa of the human penis, with α_{1A}- and α_{1D}-adrenoceptors predominating [3, 15]. The α_1-adrenoceptor agonist, phenylephrine, contracts human erectile tissue. The potencies of prazosin and yohimbine in inhibiting the responses to phenylephrine are consistent with an α_1-adrenoceptor mediated effect [16]. The selective α_2-adrenoceptor agonist, UK 14304, also contracts corpus cavernosal smooth muscle of the rabbit [17]; however, since this contraction could be blocked by both the α_1-adrenoceptor antagonist prazosin, and by α_2-adrenoceptor antagonists rauwolscine and RS-15385, the adrenoceptor involved in this response cannot be conclusively established. Phenylephrine-induced contraction of human and rabbit corpus cavernosa has been postulated to involve the α_{1B}-adrenoceptor subtype [18–20].

The Putative α_{1L}-Adrenoceptor in Urogenital Tissues

The concept of an atypical α_1-adrenoceptor having relatively low affinity for prazosin was initially proposed by Flavahan and Vanhoutte [21], and extended by Muramatsu and co-workers [22–24]. This receptor, designated as the α_{1L}-adrenoceptor, may mediate, in part, the contractile response to norepinephrine in blood vessels of several species [24]. In addition, the lack of complete correspondence between potency of antagonists in prostatic smooth muscle and affinity for recombinant α_{1A}-adrenoceptors has been explained by assuming that prostate contraction is mediated, at least in part, by the α_{1L}-adrenoceptor. It appears that most α_1-adrenoceptor antagonists have nearly equivalent affinity for α_{1A}- and α_{1L}-adrenoceptors, which could explain the good general correlation that has been observed between activity in the prostate and affinity for the α_{1A}-adrenoceptor.

Despite extensive efforts, the α_{1L}-adrenoceptor has not been cloned, and while several splice variants of the α_{1A}-adrenoceptor have been identified, homology screening has not identified any additional novel α_1-adrenoceptors.

Table 1. Antagonist selectivity between α_{1A}- and α_{1L}-adrenoceptors

Compound	K_B (vas deferens) (nM)	K_B (canine prostate) (nM)	Ratio[a]
	20[b] [26]	0.60[b] [26]	33
Prazosin	1.7[b] [26]	26[b] [26]	0.07
	1.0[c] [27]	18[c] [28]	0.06
RS 17053	0.32[c] [29]	26[c] [30]	0.01

[a] K_B (vas deferens)/K_B (prostate).
[b] K_B determined against phenylephrine-induced contraction.
[c] K_B determined against norepinephrine-induced contraction.

Interestingly, it appears that the pharmacological characteristics of the α_{1A}-adrenoceptor can vary substantially depending upon assay conditions. In CHO cells expressing the recombinant α_{1A}-adrenoceptor, the 'α_{1A}' selective antagonist, RS 17053, shows substantially lower potency against functional responsees (phosphatidyl inositol turnover and calcium influx) in intact cells than as an inhibitor of radioligand binding to α_{1A}-adrenoceptors in membrane homogenates. Furthermore, the K_i-value for RS 17053 as an inhibitor of [^{3}H] radioligand binding to α_{1A}-adrenoceptors in these CHO cells is dependent on assay conditions, with a lower affinity observed when binding is conducted under more physiological conditions (tissue culture medium, intact cells, 37°C) than under the conditions commonly employed for radioligand binding assays (membrane homogenates, Tris buffer, 20°C). These observations have led to the proposal that the α_{1L}-adrenoceptor may not represent an independent molecular entity, but rather may be an 'affinity state' of the α_{1A}-adrenoceptor which is predominant in prostate and certain blood vessels.

The condition-dependent differences in affinity observed for prazosin and RS 17053 are only observed for the α_{1A}-adrenoceptor subtype; affinities for α_{1B}- and α_{1D}-adrenoceptors are similar under the different radioligand binding assay conditions or in functional assays. However, other antagonists, such as indoramin and tamsulosin, have virtually equal affinities for the α_{1A}-adrenoceptor under all assay conditions.

Nevertheless, there does not appear to be a quantitative relationship between the degree of α_{1A}-versus α_{1L}-adrenoceptor selectivity, and the differences observed in affinities of antagonists obtained in radioligand binding and functional studies of the recombinant α_{1A}-adrenoceptor (see review [25]). This 'affinity state hypothesis' remains to be proven by using additional antagonists with differing selectivity profiles, recombinant α_{1A}-adrenoceptors expressed in other cell lines and/or other radioligands to label the α_1-adrenoceptor.

Even if the α_{1L}-adrenoceptor does represent an affinity state of the α_{1A}-adrenoceptor, rather than a distinct gene product, it is possible that the α_{1L}-adrenoceptor can be selectively targeted with novel antagonists. While the compounds described by Meyer et al. [26] have not been extensively characterized, their profile suggests that it is possible to identify compounds that have higher affinity for α_{1L}- vis-a-vis α_{1A}-adrenoceptors, which may result in compounds that are relatively selective for prostatic tissue (table 1).

Therapeutic Applications of α-Adrenoceptor Agonists and Antagonists

Benign Prostatic Hyperplasia

1. α_1-Adrenoceptor Antagonists

Selective α_1-adrenoceptor antagonists, such as terazosin, doxazosin and alfuzosin, are now used extensively for the symptomatic treatment of benign prostatic hyperplasia. This derives from the observation that phenoxybenzamine could block the contractile activity of norepinephrine in isolated strips of rat or human prostate [31–32].

Several novel α_1-adrenoceptor antagonists have been evaluated for uroselectivity in animal models and for clinical efficacy in patients with BPH. Uroselectivity in animals can be evaluated by comparing the ability of an antagonist to block agonist-induced increases in urethral perfusion pressure or prostatic contraction to its ability to

block agonist-induced increases in blood pressure or its ability to lower basal blood pressure.

Several of the compounds that show excellent uroselectivity in animal models have been evaluated clinically in patients with BPH. There are currently no reported data to suggest that these new uroselective α_1-adrenoceptor antagonists offer clinical superiority to the non-subtype selective α_1-adrenoceptor antagonists which are currently used for this indication. While it seems reasonably certain that α_{1A}- and/or α_{1L}-adrenoceptors are responsible for contraction of the smooth muscle of human lower urinary tract in vitro, and for increasing urethral resistance in animal models in vivo, the relationship between these two α_1-adrenoceptor subtypes to the treatment of BPH is less certain. It has been postulated that α_1-adrenoceptors at other sites, such as bladder, spinal cord and efferent sympathetic neurons, may contribute to the control of micturition [33]. The magnitude of these extra-prostatic actions, and the α_1-adrenoceptor subtype(s) involved, are as yet uncharacterized. Hence it is possible that, contrary to the evidence provided by preclinical studies in animal models, a non subtype-selective α_1-adrenoceptor antagonist may provide a superior clinical profile than an α_{1A}- or α_{1L}-adrenoceptor subtype selective agent in the management of BPH.

2. α_2-Adrenoceptor Agonists

As noted above, it is possible that part of the beneficial action of an α_1-adrenoceptor antagonists in BPH results from inhibition of activity in the sympathetic nerves innervating the prostate [34–35]. Inhibition of parasympathetic activity to the bladder may also be beneficial [36].

It is possible, therefore, that some or all of these neuroinhibitory actions could also be produced by an α_2-adrenoceptor agonist, acting at presynaptic receptors either at a prostatic, spinal or central location. Clonidine, which does not contract isolated strips of human prostate, will inhibit the contraction of prostatic strips induced by sympathetic nerve stimulation [37]. Prejunctional α_2-adrenoceptors also have been shown to inhibit adrenergic neurotransmission in guinea pig urethra [38] and rat bladder [39]. Cholinergic neurotransmission in the parasympathetic ganglia of rabbit bladder is also inhibited by α_2-adrenoceptor activation [40]. An α_2-adrenoceptor agonist could, theoretically, inhibit the actions of multiple neural inputs to the lower urinary tract, and hence could offer potential advantages over α_1-adrenoceptor antagonists with respect to inhibition of the dynamic component of prostatic obstruction.

Urinary Incontinence

1. α_1-Adrenoceptor Agonists

Because activation of α_1-adrenoceptors results in contraction of the vesico-urethral sphincter, α_1-adrenoceptor agonists may be useful in the treatment of stress incontinence, where the primary defect is insufficient sphincter tone to prevent urine leakage when abdominal pressure increases. Agents currently used for this purpose include the indirect acting sympathomimetic amines, such as pseudoephedrine and phenylpropanolamine, as well as the directly acting agonists, such as midodrine [41–43].

The α_1-adrenoceptor agonists currently used for stress incontinence do not differentiate between vascular and urethral α_1-adrenoceptors, and therefore increases in blood pressure may be observed with these drugs, especially at higher doses. However, in vivo [12] and in vitro [44] data support the notion that it is possible to increase selectively urethral vis-a-vis vascular tone. It has been postulated that the uroselective agonist activity observed with NS-49 results from its ability to selectively activate α_{1A}- (or α_{1L}-) adrenoceptors [12].

2. α_1-Adrenoceptor Antagonists

α_1-Adrenoceptor antagonists would be expected to exacerbate the symptoms of stress incontinence, and indeed, these compounds can induce incontinence in a small percentage of patients when used for antihypertensive therapy [15]. However, α_1-adrenoceptor blockade may be useful in reducing the excess detrusor activity observed in stress incontinence. Increased α-adrenoceptor mediated contraction has been observed in patients with an uninhibited bladder [46]. In the rat, partial bladder outlet obstruction leads to detrusor instability, with an increased frequency of non-voiding contractions. Studies with α_1-adrenoceptor antagonists have demonstrated that these non-voiding contractions could be attenuated by α_{1D}-adrenoceptor antagonists [47]. Intravenous administration of thymoxamine, an α_1-adrenoceptor antagonist will induce relaxation of the irritable bladder in patients with spinal lesions [48]. Blockade of spinal α_1-adrenoceptors may also have a favorable effect on the micturition reflex in rats with bladder outlet obstruction [34, 36].

Erectile Dysfunction

It has long been known that oral or intravenous administration of the α-adrenoceptor antagonists phenoxybenzamine and phentolamine will produce some degree of

penile erection [49]. Recent studies confirm that oral or buccal administration of phentolamine can induce full erections in approximately 50% of patients with organic impotence [50–51]. Based on large clinical trials in BPH and hypertension, it has also been noted that the incidence of impotence is significantly lower in patients treated with the α_1-adrenoceptor antagonist doxazosin, compared to placebo [52–53].

The direct application of an α_1-adrenoceptor antagonist to cavernosal smooth muscle via local injection provides a superior erection, compared to systemic therapy [49]. A mixture of papaverine, phentolamine and prostaglandin E1 (Trimix) is commonly employed [54] for this use, although monotherapy with thymoxamine, a selective α_1-adrenoceptor antagonist, has also been shown to be effective [55–56]. Combinations of prazosin and prostaglandin E1 have been shown to be effective when administered via a controlled trans-urethral delivery system [57].

Conclusion

Agents interacting with α-adrenoceptors in urogenital tissues have several important clinical applications. α_1-Adrenoceptor antagonists are now considered as firstline pharmacotherapy for benign prostatic hyperplasia. Clinical evaluation of both α_1-adrenoceptor agonists and antagonists for urinary incontinence, and α_1-adrenoceptor antagonists for erectile dysfunction, are ongoing. This interest in drugs interacting with α_1-adrenoceptors in the lower urogenital system has resulted in the characterization of the multiple roles that the α_1-adrenoceptor subtypes play in the control of urogenital function. Evidence is accumulating to indicate that the α_1-adrenoceptor subtypes may produce different responses in different urogenital tissues. Thus, the α_{1A}- (or α_{1L}-) adrenoceptor may be most important in the prostate and urethra, whereas the α_{1D}-adrenoceptor may be more critical in the bladder, and the α_{1B}-adrenoceptor may mediate smooth muscle responses in the penis. These differences could result in significant advances in the pharmacotherapy of lower urogenital disorders, such as benign prostatic hyperplasia, urinary incontinence and erectile dysfunction.

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